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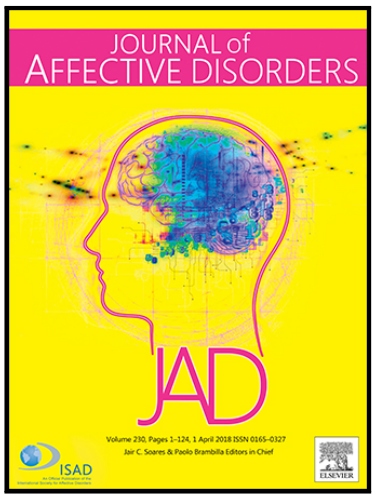


# The Relationship Between the Dietary Inflammatory Index (DII®) and Incident Depressive Symptoms: A Longitudinal Cohort Study

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**Highlights**

- Dietary inflammatory index (DII®) is a validated measure of inflammatory potential of the diet.
- Highest DII® quartile is associated with incident depressive symptoms as defined by CES-D score ⩾16 after a follow-up of 8 years in subjects at risk of arthritis (HR: 1.24; 95% CI: 1.01-1.52; p=0.04).
- Analyses were adjusted for 10 potential confounders at baseline, included age, BMI, baseline CES-d score.
- This is the first longitudinal study assessing the association between DII® and depressive symptoms in an American population.

# THE RELATIONSHIP BETWEEN THE DIETARY INFLAMMATORY INDEX (DII®) AND INCIDENT DEPRESSIVE SYMPTOMS: A LONGITUDINAL COHORT STUDY

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## ABSTRACT

Background

Diet is a common source of inflammation, and inflammation is associated with depression. We examined the association between the dietary inflammatory index (DII®), a validated measure of inflammatory potential of the diet, and risk of depression in a cohort of older North American adults.

Methods

This longitudinal study, with a follow-up of 8 years, included 3,648 participants(1,577 males, 2,071 females; mean age: 60.6 years) with/at risk of knee osteoarthritis. DII® scores were calculated using the validated Block Brief 2000 Food-Frequency Questionnaire. Center for Epidemiological Studies Depression-20 scale was used to define depressive symptoms. The relationship between baseline DII® score and incident depression was assessed through Cox's regression analysis, adjusted for potential confounders, and reported as hazard ratios (HRs).

Results

In total, 837 individuals (310 men and 527 women) developed incident depressive symptoms over the course of 8 years. Participants in the most pro-inflammatory group (quartile 4) had approximately 24% higher risk of developing depressive symptoms compared to subjects with the most anti-inflammatory diet (HR: 1.24; 95% CI: 1.01-1.53; p=0.04).

Conclusion

These results suggest that a pro-inflammatory diet may be associated with higher incidence of depressive symptoms in a cohort of older Americans. Transitioning to a more anti-inflammatory diet may reduce depression risk.

**Keywords:** depression, health behavior, neuroimmunology, old age

## INTRODUCTION

Depression is a chronic condition with an estimated lifetime prevalence of 14.6% and 11.1% in high- and lower-and-middle-income countries, respectively. (Bromet et al., 2011; Kessler and Bromet, 2013). Moreover, it is estimated that depression is one of the leading sources of disability worldwide (2015; Ferrari et al., 2013), being associated with reduced quality of life and medical morbidity (Ferrari et al., 2013; Kessler and Bromet, 2013; Rackley and Bostwick, 2012). Increasing evidence also shows that depression might confer a higher risk for several non-communicable diseases (e.g., diabetes (Rotella and Mannucci, 2013a), obesity (Luppino et al., 2010), metabolic syndrome(Vancampfort et al., 2015), cardiovascular disease (Correll et al., 2017), stroke (Tsilidis et al., 2015), acute myocardial infarction (Wu and Kling, 2016), dementia (Cherbuin and Kim, 2015) and physical health co-morbidities(Read et al., 2017)). At the same time, these chronic health conditions appear to increase the likelihood of developing depression(Bennett and Thomas, 2014; Hackett and Pickles, 2014; Lichtman et al., 2014; Luppino et al., 2010; Rotella and Mannucci, 2013b) .

There is now robust evidence to suggest that inflammation plays a pivotal role in the development of depression, and that people with confirmed depression have elevated levels of various inflammatory markers, including c-reactive protein, interlueking-6 and tumor necrosis factor (Kohler et al., 2017a; Kohler et al., 2017b) Increasing evidence has been accumulating linking diet to inflammation (Aeberli et al., 2011; Cavicchia et al., 2009). The Dietary Inflammatory Index (DII®) is a literature-derived dietary tool, useful for assessing the overall inflammatory potential of individual's diet.(Shivappa et al., 2014a) Higher DII® values are strongly associated with serum

inflammatory markers, including IL-6, hs-C-Reactive Protein (CRP), fibrinogen, homocysteine and Tumor Necrosis Factor (TNF)-α(Ramallal et al., 2015; Shivappa et al., 2014b; Tabung et al., 2015b; Wirth, 2016; Wirth et al., 2014b), suggesting a close relationship between this index and bio-humoral inflammatory parameters. The DII® has also has been used to assessed the relationship between diet quality related to inflammation and several chronic inflammation-related outcomes, such as metabolic and respiratory diseases, frailty, cancer and fractures.(Orchard et al., 2016; Shivappa et al., 2017; Tabung et al., 2015a; Wirth et al., 2014a; Wood et al., 2015) Two cross-sectional (Phillips et al., 2017; Wirth et al., 2017) and four longitudinal (Adjibade et al., 2017; Akbaraly et al., 2016; Sanchez-Villegas et al., 2015; Shivappa et al., 2016) studies have investigated the association between DII® scores and depression, showing consistent data supporting such an association from both cross-sectional and longitudinal data. DII® has not been associated with incident depression or depressive symptoms in a prospective study in American population.

Given this background, we aimed to investigate if higher DII® scores were associated with a higher risk of depressive symptoms during follow-up period (assessed through CES-d score ⩾16) in a large cohort of American people at high risk of osteoarthritis (OA), over 8 years of follow-up.

## MATERIALS AND METHODS

### *Data source and subjects*

Data were included from the Osteoarthritis Initiative (OAI) database. The OAI is freely available (http://www.oai.ucsf.edu/). Within the OAI, potential participants were recruited across four clinical sites in the United States of America (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. In this database, we identified people who either: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA (Eby and Eby, 2006) with data collected during baseline and screening evaluations in November 2008. Exclusion criteria for the OAI were: (1) Rheumatoid Arthritis (RA) or inflammatory arthritis; (2) unlikely to demonstrate measurable loss of joint space during the

study; (3) bilateral total knee joint replacement or plans to have bilateral knee replacement in the next 3 years; (4) unable to undergo a 3.0 Tesla MRI exam of the knee because of contraindications or inability to fit in the scanner or in the knee coil; (5) positive pregnancy test; (6) unable to provide a blood sample for any reason; (7) use of ambulatory aids other than a single straight cane; (8) co-morbid conditions that might interfere with the ability to participate in a 4-year study; (9) unlikely to reside in the clinic area for at least 3 years; (10) current participation in a double-blind randomized controlled trial; or (11) unwilling to sign informed consent.

All participants provided informed written consent. The OAI study was given full ethical approval by the institutional review board of the OAI Coordinating Center, at the University of California in San Francisco.

***Dietary data and Dietary inflammatory index (exposure)***

Dietary intake was assessed using a validated tool, the Block Brief 2000 Food Frequency Questionnaire (FFQ) during the baseline visit. (Block et al., 1990). Seventy items were assessed to determine an individual's typical food and beverage consumption over the past year. The frequency of consumption was reported at nine levels of intake from "never" to "every day". In addition, seven dietary behavior questions were asked regarding food preparation methods and fat intake, one question on fiber intake, and 13 questions on vitamin and mineral intakes.

The details of development of DII® is described by Shivappa *et al*. elsewhere (Shivappa et al., 2014a) . High sensitivity CRP measurements were used to examine construct validity of the DII® in a longitudinal cohort using multiple (up to 15) 24-hour dietary recall interviews and up to five 7-day dietary recalls. The DII® was subsequently validated in four studies among different populations with a variety of inflammatory biomarkers (i.e., interleukin, IL-6, hs-CRP, fibrinogen, homocysteine and TNF-α) (Ramallal et al., 2015; Shivappa et al., 2014b; Tabung et al., 2015b; Wirth, 2016; Wirth et al., 2014b). In this updated version of the DII®, 1943 articles were reviewed

and scored. Forty-five food parameters, including foods, nutrients, and other bioactive compounds, were identified based on their inflammatory effect on six specific inflammatory markers, including CRP, IL-1β, IL-4, IL-6, IL-10 and tumor necrosis factor (TNF)-α. A regionally representative world database representing diet surveys from 11 countries was used as a comparative standard for each of the 45 parameters (i.e. foods, nutrients, and other food components). Intake values from this database were used to calculate the DII® scores. This is explained in more detail in the DII® Methods paper (Shivappa et al., 2014a). Briefly, a standard mean for each parameter from the representative world database was subtracted from the actual individual exposure and divided by its standard deviation to generate Z scores. These Z scores were converted to percentile ranks (thus minimizing effects of outliers/right- skewing). These values were then doubled and 1 was subtracted to achieve symmetrical distribution with values centered on 0. The resulting value was then multiplied by the corresponding inflammatory score for each food parameter and summed across all food parameters, to obtain the overall DII® score. Using the FFQ, we calculated the DII® based on energy-adjusted intake of the 24 single food parameters of the 45 possible food parameters that were available from the FFQ using the energy density approach, which calculated the DII® per 4184 kJ (1000 kcal) of energy (Willett et al., 1997). The 24 food parameters available for DII® calculation in this study were vitamin $B_{12}$, vitamin $B_6$, β-carotene, carbohydrate, cholesterol, fat, fibre, folic acid, iron, magnesium, monounsaturated fat acids (MUFA), niacin, protein, polyunsaturated fatty acids (PUFA), riboflavin, saturated fat acids(SFA), selenium, thiamin, vitamin A, vitamin C, vitamin E, vitamin D, zinc, and caffeine.

***Outcome***

The presence of depressive symptoms was derived from the 20-item Center for Epidemiologic Studies-Depression (CES-D) instrument (Radloff, 1977). The range of possible values for this scores is 0 to 60, where higher scores indicate more depressive symptoms. (Radloff, 1977) A cut-off of 16 was used for the diagnosis of incident depressive symptoms.(Veronese et al., 2016)

***Covariates***

Eleven covariates (other than baseline CES-D) were identified *a priori* as potential confounding factors. These included: age; sex; body mass index (BMI); physical activity evaluated using the total score for the Physical Activity Scale for the Elderly scale (PASE) (Washburn et al., 1999); race; smoking habit; educational attainment level (college or higher vs. others); yearly income (< or ≥ $50,000 or missing data); statins use; NSAIDs or cortisone use; and a validated general health measure of self-reported comorbidities assessed through the modified Charlson Comorbidity Index score.(Katz et al., 1996)

***Statistical analyses***

Data on continuous variables were normally distributed according to the Kolmogorov-Smirnov test. Data were presented as means and standard deviation values (SD) for quantitative measures, and frequency and percentages for all discrete variables. Levene's test was used to test the homoscedasticity of variances and, if its assumption was violated, Welch's ANOVA was used. P-values were calculated using the Jonckheere-Terpstra test (Jonckheere, 1954) for continuous variables and the Mantel-Haenszel Chi-square test for categorical variables.

To assess the relationship between DII® score and incident depressive symptoms, a Cox's regression analysis was conducted where the incident depressive symptoms were defined as the discrete 'outcome,' time-to-event was the temporal factor, and the DII® score was the 'exposure'. The basic model was not adjusted for any confounders. The fully adjusted model included the following covariates: age (as continuous); sex; race (Whites vs. others); BMI (as continuous); education (≥college degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as ≥ or < US$50,000 or missing data); Charlson Comorbidity Index; PASE score (as continuous); CES-D at baseline (as continuous); statins use (yes vs. no); NSAIDS or cortisone use (yes vs. no).

Multi-collinearity among covariates was assessed through variance inflation factor (VIF) (Miles, 2009), taking a cut-off of 2 as the criterion for exclusion. No covariates met this criterion and therefore none was excluded for this reason. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated to estimate the strength of the associations between DII® score (reported as quartiles) and incident depressive symptoms. P values for trend were calculated across DII® groups using the Wald test, based on a score derived from the median value of each baseline DII® group. We finally modelled DII® score as a continuous variable, reporting the association between increase in one SD as the exposure variable.

A $p<0.05$ was deemed statistically significant. All analyses were performed using SPSS® software version 21.0 for Windows (SPSS Inc., Chicago, Illinois).

## RESULTS

### *Sample selection*

The OAI dataset initially included a total of 4,796 individuals. A total of 264 participants were excluded due to missing baseline data regarding CES-D and 462 were excluded for having depressive symptoms (i.e. CES-D >16) at baseline. In addition, we were not able to compute DII® scores for another 278 individuals (80 participants had too many missing data for us to compute a DII® score, and another 198 participants reported consuming total energy outside of the protocol-required acceptable range; i.e., less than 800/greater than 4200 Kcal for men and less than 500/greater than 3800 for women). Thus, 3,608 participants were included in this study.

### *Descriptive characteristics*

The cohort consisted of 2,037 females (56.5%). Mean age was 61.4 years (±9.2 years; range: 45-79 years) and mean DII® was -3.25 (±1.61 points; range: -5.54 to 3.57).

**Table 1** illustrates the baseline characteristics by DII® quartiles in the sample as whole. Those in the highest DII® quartile (reflecting the most pro-inflammatory diets) were significantly younger and more frequently males than participants with lower DII® values (p for trend <0.0001). The participants with higher DII® values at baseline were more frequently smokers (p for trend=0.001), less educated (p for trend=0.002), more frequently obese (p for trend <0.0001), and used less frequently statins (p for trend <0.0001).

Finally, people with higher DII® values reported significantly higher baseline values at CES-D (p for trend <0.0001) (**Table 1**).

### *Dietary inflammatory index and incident depressive symptoms*

Over a mean follow-up of 8 years, 837 individuals (310 men and 527 women; = 23.2% of the baseline population) had depressive symptoms, for a global incidence of 39 (95%CI: 36-41) people for 1,000 persons-years. The incidence of depressive symptoms was significantly higher in people

having higher DII® values at baseline (Q4: 45; 95%CI: 40-51 vs. Q1: 32; 95%CI: 28-37; p<0.0001) (**Table 2**).

Cox's regression analysis, adjusting for 12 potential confounders at baseline, with the lowest DII® as reference (=Q1), showed that participants with the highest DII® score (=Q4) had a significantly higher probability of incident depressive symptoms (HR: 1.24; 95% CI: 1.01-1.53; p=0.04; **Table 2, figure 1**). However, the p for trend did not reach the statistical significance (p=0.10). An increase in one SD of DII® (=1.61 points) did not increase the risk of depressive symptoms at follow-up (adjusted HR=1.02; 95%CI: 0.96-1.09; p=0.52).

In the multivariate analysis, other factors significantly associated with the onset of depressive symptoms during follow-up were: female sex (HR=1.23; 95%CI: 1.06-1.44; p=0.008), higher BMI (HR: 1.02; 95% CI: 1.006 to 1.04; p=0.007), and higher CES-D (HR: 1.19; 95% CI: 1.17 to 1.21; p<0.0001).

We also conducted multiple *post-hoc* sensitivity analyses in order to evaluate the interaction between DII® score and selected participant characteristics [i.e., age ≤65 years, overweight/obese (≥25kg/m$^2$) vs. normal weight (18.5kg/m$^2$<BMI ≥25kg/m$^2$), yearly income, gender, race, education, smoking habits, yearly income, presence at baseline of knee OA] in the association with incident depressive symptoms, but none emerged as moderator of our findings (p>0.05 for the interaction for all factors).

## DISCUSSION

In this longitudinal study, we found that a more pro-inflammatory diet intake (indicated by higher DII® scores) was associated with greater incidence of depressive symptoms as defined by CES-D ⩾16. During a follow-up period of 8 years, after adjusting for several potential confounders at baseline, individuals with the highest DII® score (i.e. having a more pro-inflammatory diet) had a 24% higher risk of depressive symptoms (p=0.04) compared with those with the lowest DII® score. At baseline, people with higher DII® scores, already had a higher prevalence of known risk factors for depression during follow-up such as lower education (Bjelland et al., 2008), obesity (Luppino et al., 2010), and higher CES-D values. However, all our analyses are adjusted for these confounders and the results remain still significant. Our findings agree with those already present in literature. In a cohort study of 15,093 university graduates, participants in the highest quintile of DII® reported a significant higher risk of depression of about 50%. (Sanchez-Villegas et al., 2015) A substantial similar finding emerged from another study involving a total of 6,438 women with a mean age of 52.0 years at baseline, followed-up over 12 years (Shivappa et al., 2016). However, it is of interest that a more recent study failed to find any significant association between baseline DII® values and incident depressive symptoms in 3,523 young participants followed-up for 12.5 years(Adjibade et al., 2017), indicating that other studies are needed to better highlight the association between DII® and depression. Altogether these findings probably indicate that the DII® is a better predictor of depression and depressive symptoms in older than younger people, probably because older people have had greater cumulative exposure to DII® than younger subjects during their lives. However, further research is needed to confirm this association.

It is widely known that inflammation is associated with depression. In the early 1990's, the macrophage theory for depression was first hypothesized (Smith, 1991), particularly when these cells are activated by any damage (M1 cells). Increasing evidence showing a role of M1 cells (including microglial cells and central nervous system macrophages) in depression has accumulated

(Yirmiya et al., 2015), because the peripheral M1 cells could be a main source of elevated cytokines in depression.(Wohleb et al., 2016) Moreover, other evidences reported that subsets of patients with depression have an altered peripheral immune system, with impaired cellular immunity and increased levels of proinflammatory cytokines, such as cytokines might influence neurotransmitter metabolism, neuroendocrine function and regional brain activity and all these factors may be relevant for the onset of depression (Wohleb et al., 2016; Zunszain et al., 2013). However, it should be noted that in the studies that adjusted their analyses for serum levels of cytokines, DII® remains significantly associated with the onset of depression.(Sanchez-Villegas et al., 2015; Shivappa et al., 2016) These findings probably suggest that unhealthy (pro-inflammatory) diet independently contributed to the onset of depression, consequently resulting in important clinical consequences. Diet seems to be an important target for the prevention of depression.(Sanchez-Villegas and Martínez-González, 2013) Some observational studies reported that healthy diets (such as Mediterranean one) are associated with a lower incidence of depression in adults. (Sanchez-Villegas and Martínez-González, 2013) Our study further reinforces these findings suggesting that healthy diets are probably necessary for the prevention of depression. Indeed, a recent RCT(Jacka et al., 2017) in adults experiencing depressive symptoms showed that adoption of the Mediterranean diet significantly reduced depressive symptoms. Moreover, a synergic anti-inflammatory action may be hypothesized, between antidepressants (Kohler et al., 2017b), and Mediterranean or macrobiotic diet, opening the field to potential preventive interventions, or early interventions that could target inflammatory pathways before or when minimal symptoms have presented. In addition, the gut-brain-axis may play a role in depression onset interacting with pro-inflammatory diet, which may contribute to the leaky gut and increased bacterial translocation in depression itself, as well as in other diet-related conditions such as diabetes and obesity (Slyepchenko et al., 2016).. Well-designed and conducted RCTs targeting gut as a treatment target with probiotics for depression are definitely needed; and this should entail a shift from healthy populations to studies conducted in clinical populations (Ng et al., 2018).

Further interventional studies are, however, needed to confirm these findings, at least in subjects with evidence of pro-inflammatory state. Also, in addition to avoiding a pro-inflammatory diet, prevention and treatment of depression can not ignore healthy life style including regular physical exercise, and avoiding recreational drugs which in turn are associated with inflammation (Fuster et al., 2015; Ghazavi et al., 2013; Gonzalez-Reimers et al., 2014).

The results of our research should be considered in light of its limitations. The principal shortcoming is that we used a definition of depressive symptoms based only on CES-D, without accounting for other aspects of depression or for the use of medications. This could introduce an important bias in our results. Second, the comorbid medical conditions assessed in this study were self-reported. Another limitation could be the non-availability of data on the remaining 21 food parameters of the DII®. Some components such as turmeric, saffron and eugenol are not consumed in high quantity in this population; so, non-availability of these food parameters may not have played major role in this association. However, inclusion of parameters such as flavonoids, which are commonly consumed, may influence the results. Third, in the OAI data on serum concentrations of inflammatory markers inflammatory parameters were not collected. Therefore, we cannot adjust for these potential confounders. Finally, the findings derived from the OAI are not fully generalizable to other populations because this database includes only people having, or at high risk of knee OA.

In conclusion, higher DII® scores were associated with a higher incidence of depressive symptoms, even after considering several potentially important confounders measured at baseline. Future randomized controlled trials with diets rich in anti-inflammatory compounds are needed to further confirm our findings.

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**Conflict of interest**: Dr. JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. NS is an employee of CHI.

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**FIGURE LEGEND**

**Figure 1. Association between Dietary Inflammatory Index (expressed in quartiles) and incident depressive symptoms, adjusted for potential confounders.**

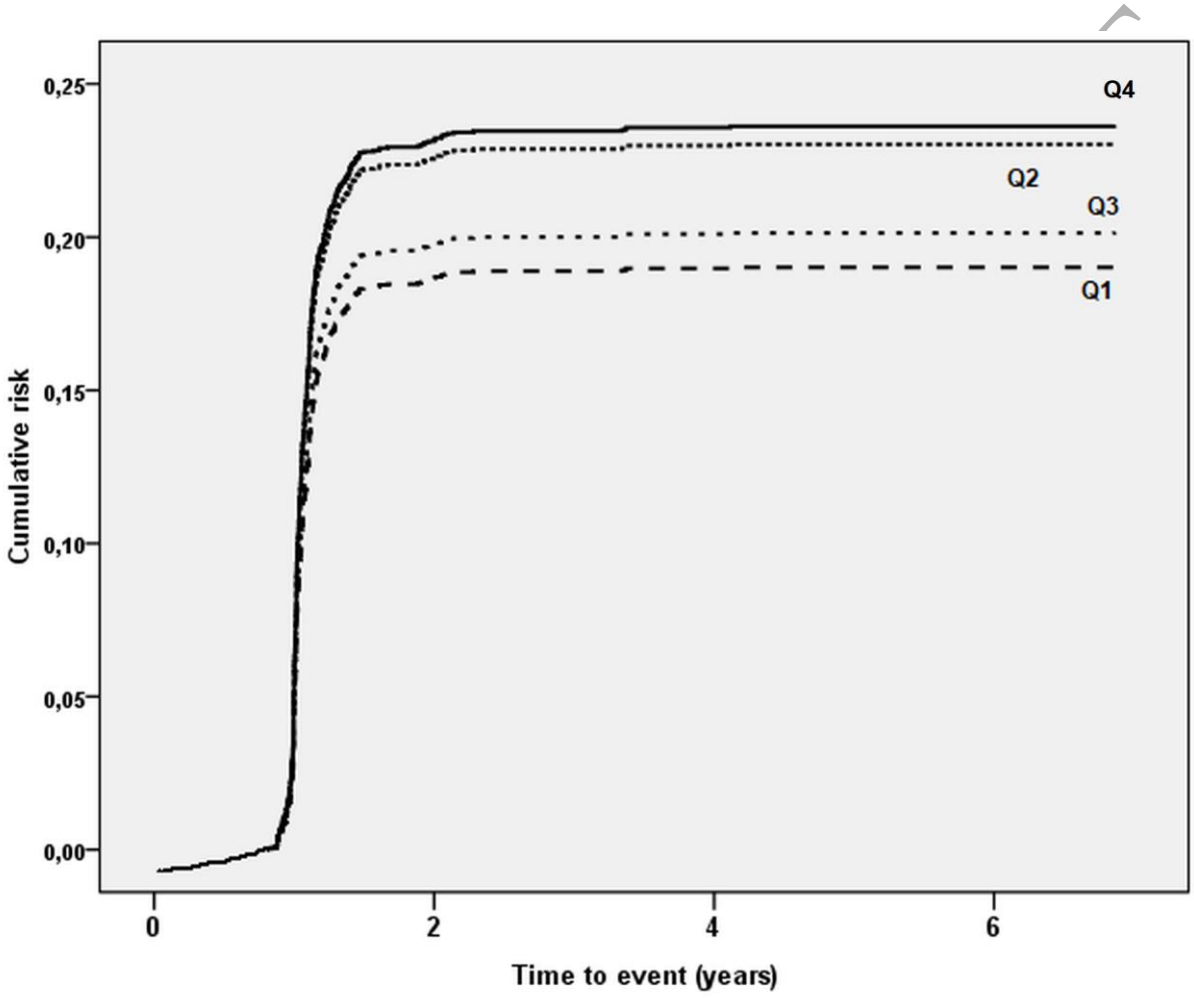

**Table 1. Characteristics of the participants classified according to their baseline dietary inflammatory index,** Osteoarthritis Initiative (OAI), 2004-6**.**

| | **Q1 (n=902) DII** | **Q2 (n=902) DII** | **Q2 (n=902) DII** | **Q4 (n=902) DII** | **p-value [a]** |
|---|---|---|---|---|---|
| ***General characteristics*** | | | | | |
| **Age (years)** | 63.2 (8.7) | 62.2 (9.2) | 61.1 (9.2) | 58.9 (9.0) | <0.0001 |
| **Females (n, %)** | 638 (70.7) | 562 (62.3) | 463 (51.3) | 374 (41.5) | <0.0001 |
| **PASE (points)** | 163 (79) | 165 (83) | 159 (82) | 168 (82) | 0.15 |
| **White race (n, %)** | 748 (83.1) | 756 (83.8) | 774 (85.8) | 718 (79.7) | 0.14 |
| **Smoking (previous/current) (n, %)** | 388 (43.0) | 406 (45.0) | 427 (47.3) | 456 (50.6) | 0.001 |
| **Graduate degree (n, %)** | 323 (35.8) | 311 (34.5) | 286 (31.7) | 267 (29.6) | 0.002 |
| **Yearly income (≥ $50,000)** | 331 (36.7) | 321 (35.6) | 290 (32.2) | 328 (36.4) | 0.53 |
| ***Medical conditions and medications*** | | | | | |
| **BMI (Kg/m$^2$)** | 27.3 (4.5) | 28.2 (4.4) | 28.9 (4.6) | 29.8 (4.8) | <0.0001 |

**Table 2. Association between dietary inflammatory index and incidence of depressive symptoms,** Osteoarthritis Initiative (OAI), 2004-6**.**

**.**

| | **Incidence (* 1,000 persons-years) (95%CI)** | **Unadjusted HR (95%CI)** | **P value** | **Fully adjusted[a] HR (95%CI)** | **P value** |
|---|---|---|---|---|---|
| **Q1** | 32 (28-37) | 1 [reference] | | 1 [reference] | |
| **Q2** | 39 (34-45) | 1.19 (0.97-1.44) | 0.09 | 1.20 (0.99-1.47)1.21 (0.99-1.48) | 0.067 |
| **Q3** | 39 (34-44) | 1.15 (0.94-1.40) | 0.17 | 1.06 (0.86-1.3029) | 0.5861 |
| **Q4** | 45 (40-51) | 1.32 (1.09-1.60) | 0.005 | 1.24 (1.01- | 0.04 |